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Early Adversity and the Neotenous Human Brain

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Abstract

Human brain development is optimized to learn from environmental cues. The protracted development of the cortex and its connections with subcortical targets has been argued to permit more opportunity for acquiring complex behaviors. This paper uses the example of amygdala-medial prefrontal cortex circuitry development to illustrate a principle of human development - namely, that the extension of the brain's developmental timeline allows for the (species-expected) collaboration between child and parent in co-construction of the human brain. The neurobiology underlying affective learning capitalizes on this protracted timeline to develop a rich affective repertoire in adulthood. Humans are afforded this luxuriously slow development in part by the extended period of caregiving provided by parents, and parents aid in scaffolding the process of maturation during childhood. Just as adequate caregiving is a potent effector of brain development, so is adverse caregiving, which is the largest environmental risk factor for adult mental illness. There are large individual differences in neurobiological outcomes following caregiving adversity, indicating that these pathways are probabilistic, rather than deterministic, and prolonged plasticity in human brain development may also allow for subsequent amelioration by positive experiences. The extant research indicates that the development of mental health cannot be considered without consideration of children in the context of their families.

Keywords

brain development; amygdala; medial prefrontal cortex; stress; sensitive periods; parents

Decades of research have demonstrated parents' critical role in the healthy development of complex cognitive and affective behaviors (1–6). Caregiving is a potent effector of human development, and therefore the reach of maltreatment on behavioral and brain development can be long and significant. Early caregiving adversities, including abuse (physical, sexual, and emotional), neglect (emotional, failure to provide, and lack of supervision), and exposure to violence in the home, have been associated with altered neurodevelopment (7–9). The current paper discusses how characteristics of human brain development might foster the endurance of these links.

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The Neotenous Brain.

The link between adverse caregiving and brain development is not unique to humans, and animal models have established that the link is causal (described below). However, humans do stand out, perhaps more than any other species, as a result of their neotenous brain development (see Figure 1). Originally coined to describe the retention of juvenile physical traits into adulthood (e.g., eruption of teeth, physical features) (10), neotenous development (or 'juvenilization') might describe human brain development as well, particularly for complex process like cognition and emotion. For example, the slow developing prefrontal cortex has demonstrated synaptic reorganization (overproduction and synapse elimination) until the third decade of life (11), well beyond what has been observed in the developmental equivalent in other mammals. Similarly, mRNA expression in the prefrontal cortex is developmentally delayed in humans relative to other primate species (12) indicating that neoteny is observed at the transcriptome level. Neoteny at the behavioral level (e.g., delayed cognition, extended play behaviors) has been described as adaptive in that it permits repeated, slow, and thus, enhanced learning opportunities (13). Scholars have speculated that there is value to this prolonged process, such that it allows for the "unprecedented opportunity for acquisition of the highest level of cognitive abilities (13)." At the same time, this characteristic of human development, which produces cognitive and affective complexity, can also increase the risk for poor outcomes following early adverse experiences.

Collectively, these papers argue that humans, more than other species, depend on learning from a very complex environment to produce rich behavioral repertoires, and a delayed onset of adult phenotypes provides more opportunities for learning these repertoires and developing strategies appropriate to the given environment. This prolonged development is comprised of multiple sensitive periods (14, 15), which are developmental moments when the environment has an especially potent and enduring impact on developing neurobiology. Moreover, the brain develops in a hierarchical fashion, where the structure and function of earlier developing regions exert maturational consequences on the structure and function of later developing regions. Referred to as 'developmental cascades' (16), such an organization implies that earlier occurring changes to the brain would have an impact not only on the neurobiology undergoing its sensitive period, but also on the downstream targets that receive connections from these regions (14, 17). Lesion work in non-human primates has illustrated this hierarchical organization; for example, neonatal lesions of the earlier developing amygdala and surrounding temporal lobe causes aberrant development of the prefrontal cortex (18); in other words, the prefrontal cortex might exhibit altered development despite the fact that is was never directly perturbed by the environment, by virtue of the fact that it is a developmental target of the earlier developing regions. Notably, the same lesions performed in adulthood did not produce these effects. These developmental principles of hierarchical development, sensitive periods, and prolonged development are critical tools for understanding the role of early experiences on adult functioning.

Amygdala-mPFC Development: Neoteny, Plasticity, and Learning.

Human amygdala-medial prefrontal cortex (mPFC) circuitry is central to mature emotional behaviors including learning, attention, modulation, and prediction (19–22). We focus on this circuitry to examine principles of neoteny and development as they relate to early caregiving adversity. While several other circuits have shown correlations with early adversity, including hippocampus, amygdala, striatum, cerebellum, and cortex (e.g., 23–25), as well as alterations to the connections between these regions, the current paper is motivated to focus on amygdala-mPFC circuitry by several of its characteristics. First, amygdala-mPFC circuitry constitutes the foundation for behaviors associated with emotion regulation in adulthood (19), behaviors which are commonly affected by early life stress. Secondly, the amygdala is rich with stress hormone receptors, especially early in life, and it exhibits membrane potential characteristics early in development that make it highly reactive to stressors (26, 27). Thirdly, amygdala-mPFC circuitry is highly sensitive to environmental influences during development, as has been demonstrated by a resting-state functional magnetic resonance imaging twin study performed during childhood (28). Additionally, the hierarchical relationship between the amygdala and the mPFC provide fodder for a deeper discussion of principles of developmental cascades.

Findings from Rodents.

Evidence from several sources shows that the structural and functional connections between the amygdala and the mPFC develop very slowly across mammalian species. Using tracing methods, rodent studies have shown that fibers originating in basolateral amygdala that project to regions of the mPFC (including the anterior cingulate, paralimbic cortex, and infralimbic cortex) exhibit a continued increase in density, spine formation, and change in topography continuing into the late postweanling/juvenile periods, perhaps even extending into adulthood (29, 30), thus occurring much later than projections to other regions (e.g., thalamus, nucleus accumbens) (31). In adulthood, amygdala-mPFC connections the are strongly bidirectional, and the development of reciprocal connections from mPFC to amygdala are late occurring; initial amygdala-to-mPFC growth spurts are later followed by even later-occurring mPFC-to-amygdala connection development (32). By combining anatomical tracings with opto-genetic interrogation, it has been shown that early bursts of growth in infancy are subsequently followed by an additional burst observed in the late juvenile/early adolescent period (33). This trajectory for structural development is paralleled by an initial burst in inhibitory post-synaptic potentials (relative to excitatory) in the late infancy period, and a second burst of inhibitory tone in the late juvenile period. This juvenile period has also been shown to be the time when the dendritic trees within amygdala and mPFC exhibit their largest growth (34). Consistent with this structural growth pattern, GABA-ergic transmission in the amygdala shows continued maturation until the end of the juvenile period (35). These data suggest that the excitatory/inhibitory balance of this pathway shows a protracted development, with an increasing shift towards top-down inhibition that does not mature until adolescence. The timing of mPFC-to-amygdala synapse formation (i.e., the juvenile period (postnatal day 30), which is roughly right after weaning yet prior to puberty (36)) coincides with a normative decline in emotionality (37, 38) and the largest developmental increase in spontaneous synaptic activity of the amygdala (33). This

finding is consistent with the hypothesis that strong activity in the amygdala instigates connection formation with the mPFC (17). Taken together, the rodent work has shown amygdala-mPFC circuitry constructs itself first in a bottom-up fashion (i.e., amygdala-to-mPFC); then strong excitatory activity from the amygdala temporally correlates with the beginning of the reciprocal top-down inhibitory connections that continue to strengthen into adulthood.

Findings from Humans.

Studies in humans suggest an analogous, albeit further protracted, late development of amygdala-mPFC connectivity, occurring across childhood and adolescence (Figure 1). For example, diffusion tensor imaging techniques have shown that fronto-temporal tracts, like the cingulum and uncinate fasciculus, mature later than other tracts, requiring 25 years to reach 90% of their development . By comparison, other large tracts, like those that connect occipital to temporal cortex reach 90% of their development already by 11 years old (39). Correlated activity between the amygdala and mPFC, or functional connectivity, parallels these fronto-temporal structural tracts (40). Functional connectivity can be measured during resting state (i.e., intrinsic connectivity) or during task (i.e., stimulus-elicited). Resting state studies performed during human development have shown that amygdala-mPFC functional connectivity continues to show developmental changes until early adulthood. Resting-state functional connectivity between the amygdala and mPFC is present during infancy (41), although it exhibits non-linear changes (increases in the first year, followed by decreases in the second year)(42). These early developments are followed by continued change throughout the next two decades, with some studies showing continued increases in connectivity from childhood through adulthood (43, 44) and others showing decreases across this period (45).

Amygdala-mPFC resting-state functional connectivity is developmentally predicted by stimulus-elicited functional connectivity recorded earlier during childhood (46), suggesting that the nature of early environmentally-stimulated coactivation of the amygdala and mPFC during childhood might have an enduring influence on the nature of its intrinsic connectivity later in maturity (17). This interpretation is consistent with findings from a behavioral-genetics study showing that individual differences in amygdala-mPFC intrinsic functional connectivity during development are best explained by environmental influences (28). Stimulus-elicited, or task-based, functional connectivity studies have also shown age-related changes in amygdala-mPFC connectivity throughout the first 3 decades of life (47–51), though these connectivity patterns vary as a function of the task. Many of these studies have shown that the nature of the relationship between the amygdala and mPFC differs in childhood relative to points thereafter (52, 53), and is unlikely to include “top-down” regulatory connections.

As was found in rodent models, the developmentally late onset of the regulatory connections between the mPFC and the amygdala temporally parallel elevated amygdala reactivity that attenuates with increasing age (47, 49, 50, 54, 55), which is consistent with the hypothesis that the juvenile-like lability of the amygdala is an important instigator for the formation of connections with the mPFC (17). Again similar to rodent findings, in the human these events

occur during late childhood into adolescence. Behaviorally, these neurobiological transitions are paralleled by the young child exhibiting high emotional reactivity and elevated levels of developmentally-normative fears (47, 56–58), and at later ages (e.g., adolescence and adulthood), these behaviors attenuate when structural and functional connections with the mPFC correspond with better regulation of the amygdala (22, 59). Taken together, studies in humans show patterns of amygdala-mPFC development that are highly consistent with those patterns identified in the rodent - namely, human development shows strong amygdala activity and emotionality early in life, followed by adult-like amygdala-mPFC connections and associated declines in emotionality at older ages - albeit occurring at a much more protracted rate.

The Ecology of the Developing Child.

The neurodevelopmental pattern of amygdala-mPFC circuitry described thus far, in many ways, mirror the ecology of the developing child (60). During a time when parents or other caregivers are routinely available to guide children's exploration, it may be ontogenetically unnecessary (and even inefficient) to mature this system early, since the role of the amygdala and its connections with the mPFC is to facilitate independent exploration of the environment (judging the safety and danger of encountered stimuli) and adult-like learning. That is, the parent provides significant, and perhaps sufficient, information about the affective environment and will continue to serve this role until physical independence from the parent becomes routine.

Parental modulation of early emotional learning.

Evidence for this claim comes from both rodent and human studies. In rodents, it has been shown that the dam's presence promotes her offspring's preference for cues associated with the dam, regardless if the stimulation is pleasurable or aversive (61). In the context of aversive cues, the dam buffers stress responsive systems (e.g., the amygdala) to paradoxically promote preference learning for her cues, and this process is the basis for attachment learning in rodents. Young children have also been shown to behaviorally prefer an aversive conditioned stimulus if acquisition occurred in the presence of their parent (62). These findings suggest a mechanism by which children learn to prefer and attach to parental cues, regardless of warmth or maltreatment (63, 64) and suggest that early emotional learning systems are constructed to allow for modification by the parent.

The normative presence of parents and caregivers is a powerful effector of development, providing a social scaffolding for the developing child. Thus, parental presence may also be scaffolding amygdala-mPFC circuitry. Providing support for this position, parental stimuli can produce a momentary adult-like amygdala-mPFC connectivity pattern in children, a modulation that coincides with a decrease in amygdala activity (65). However, at the transition between childhood and adolescence, this circuitry changes and begins to show adult-like 'regulatory' connectivity patterns, regardless of parental cue presence or absence. During adolescence, parental presence may be less necessary (and also less effective) in modulating this circuitry, which has now become more adult-like (47). However, there may

still be times in adolescence when the parent retains their 'buffering' effects, for example under conditions of risky-decision making (66).

Normative Variation in Parenting Behavior: Sensitivity and Security.

Parental care has been shown to correlate with the nature of amygdala-mPFC circuitry structure and function across a number of studies. For example, studies have shown that attachment styles, when measured in adulthood, are correlated with concurrent amygdala function (67, 68); moreover, when attachment is measured in infancy, these classifications have predicted amygdala structural differences when measured years later in childhood (e.g., 10 years old)(69) and even into adulthood (70, 71). Attachment security is thought to reflect parenting quality received (72), and these enduring associations between attachment style and amygdala development may reflect the discrete, routinized parenting behaviors experienced during childhood (73). Indeed, parenting quality itself has been correlated with amygdala and prefrontal cortex development. For example, parental sensitivity during infancy has been associated with smaller amygdala volumes (74); when measured during childhood, parental sensitivity has been shown to moderate age-related increases in amygdala-mPFC resting-state connectivity, with the suggestion that low sensitivity accelerates development of functional connections (75). In fact, early parenting behavior has predicted amygdala-mPFC circuit development across a span of years (76–79). If the links between parental care and amygdala-mPFC development are not only predictive, but also causal in humans as they have been shown to be in rodent models, these pathways not only increase the risk for internalizing problems (80, 81), but also for peer relationships (82) and future parenting behaviors (83). Taken together, these findings support the hypothesis that sensitive parenting and the associated security established in offspring are effective in influencing the nature of amygdala-mPFC circuitry function in maturity.

Caregiving Adversity.

Characterizing the link between individual differences in normative caregiving and amygdala-mPFC circuitry development provides important insights into the profound impact that caregiving adversities have on emotional development and psychopathology risk, as well as the mechanisms by which these experiences exert their effects. Mental health is dependent on adequate caregiving (4, 84), and indeed adverse caregiving is associated with increased odds for mental health problems (85–87) including externalizing and internalizing disorders that can emerge in adolescence (88), and mood, anxiety, and personality disorders that can last into old age (89). Although these mental health outcomes generally involve difficulties in emotion regulation, the specific diagnoses may reveal themselves in sex-specific ways (especially after puberty) (90), in part because of gonadal differences that emerge during this time (91), differences in amygdala development between boys and girls (92, 93), and perhaps differences in the types of maltreatment that girls may experience from boys (94). Caregiving adversity is a highly-potent stressor for the central nervous system, occurring during the brain's most vulnerable period. This vulnerability is conferred by the numerous sensitive periods occurring throughout the first two decades of life that render neurobiological systems more or less amenable to environmental pressures in a time-specific manner (91, 95, 96), the cellular properties of the developing amygdala that increase its

sensitivity and reactivity to stress, and the hierarchical nature of brain development, which can engender cascading effects of early life stress onto later developing circuits.

Findings from the non-human animal literature.

A large animal literature has established a causal role for adverse caregiving (e.g., abuse, maternal separation, exposure to maternal distress) in prematurely activating amygdala (97, 98), promoting earlier growth and myelination of amygdala cells (99, 100), amplifying amygdala excitability (101), increasing synaptic density in layer II of the infralimbic cortex (102), instantiating earlier use of mature extinction (103) and contextual fear conditioning (in male rodents) (104), and later reducing adolescent plasticity in mPFC and connectivity between amygdala and mPFC (105–107). These accelerations have been described as ontogenetic adaptations (108–110). Ontogenetic adaptations can only occur with the biological premise of developmental plasticity. In the context of developmental plasticity, activity-based processes might promote maturation of these affective circuits (as has been shown in other domains) (109, 111). Accelerating the development of amygdala-mPFC circuitry may be beneficial for young animals who have received cues of danger or abandonment in that the young animal is able to navigate stressors and threats independently to some degree (but presumably, not nearly as effectively as the adult can). That is, cues from the environment signaling inadequate caregiving may motivate a change in developmental strategies. However, accelerated development might, at the same time, truncate growth processes, thereby attenuating developmental plasticity (104), which could have deleterious consequences on later functions that depend on learning and slow growth during early sensitive periods.

Findings from the human literature.

The neotenous development of the human brain renders it vulnerable to psychosocial adversities for a prolonged period. That is, because we retain plasticity for an extended period, there is a wide window during which early life stressors can take hold. Whether early life stress produces accelerations in human brain development, or not, is not yet clear. However, there are emerging findings across studies suggestive of accelerated development. In addition to the more “mature-like” findings described above in instances of insensitive caregiving (within the normative range), extreme caregiving neglect, in the form of institutional caregiving, as well as exposure to violence (to self or other) has been associated with patterns of task-based amygdala-mPFC connectivity that more closely resemble adult patterns than child patterns (112, 113). Additionally, in the context of more normative family stressors, childhood adversity is associated with augmentation of prefrontal-subcortical circuits (114). Prenatal maternal depression has also been associated with patterns of amygdala-mPFC resting state connectivity in infants that have been interpreted as accelerations (115). Despite these initial findings, it is too early to firmly conclude that early psychosocial adversity accelerates human amygdala-mPFC development, and current findings require replication and expansion. However, if this hypothesis continues to receive support, it would call to mind Waddington’s epigenetic landscape metaphor (116), presenting multiple pathways (some more desirable than others) of development, that lead to the adult form. Accelerated development may be a preferred path under conditions of early

stress, but are less desirable in the long run, perhaps because of increased risk for mental health problems.

The mechanistic pathways by which early life stress operates in humans have not yet been identified with certainty, but the large number of studies identifying correlations between adverse caregiving and altered amygdala-mPFC development is noteworthy. For example, while the amygdala in infancy does not typically seem to increase activity for emotional stimuli (117, 118), the amygdala can be recruited in infants exposed to domestic violence (119). Growing up with parental psychopathology, exposure to domestic violence, severe neglect, including institutional care in infancy, and/or physical/sexual abuse has been associated with alterations in amygdala development and connections between the amygdala and mPFC (112, 120–128). Although there is consistency across studies in that amygdala and mPFC commonly emerge as neurobiological targets of adversity, there are inconsistencies across studies in terms of the nature of the effects, particularly with regard to volume. These discrepancies may result from the unique aspects of the maltreatment experiences under investigation (e.g., threat versus deprivation of a stimulus(7); emotional/psychological harm versus physical harm, etc.). There is some promising evidence that different subtypes of maltreatment may target different developmental outcomes (129, 130). However, there are also adversity-related phenotypes that transcend subtype (e.g., 131, 132), suggesting that some behavioral domains exhibit *developmental equifinality* - that is, disparate adverse experiences nonetheless leading to the same final common pathway (133). At the same time, it is difficult to draw conclusions about the source of discrepancies because the importance of age is not always fully recognized; it is possible that effects of caregiving adversity change as a function of age at test or as a function of age of adversity exposure (9, 131). For example, studies that have observed larger amygdala volumes following early life adversity tend to examine children (120, 134), whereas those that identify smaller amygdala volumes tend to include adolescents (132, 135). One hypothesis by Teicher et al. (2016) (8) predicts that early life stress produces initial enlargements of amygdala volume, which then sensitize it to subsequent stressors, resulting in a volume reduction later in life. Thus, developmental changes in neurobiology should be considered seriously in studies of early adversity (e.g., 136) because findings in childhood may differ from those observed in adolescence and adulthood.

Heterogeneity and resilience following early adversity.

Despite these many findings linking caregiving adversities to altered amygdala-mPFC circuit development, there are large individual differences in brain development. The mental health outcomes associated with amygdala-mPFC development also exhibit significant heterogeneity (137), and many youth exhibit psychological resilience despite exposure to adversity. This heterogeneity evokes notions of *developmental multifinality,* which describes divergent developmental pathways for two individuals who begin with similar risk (133). Nonetheless, the sources of these individual differences require much more research. We do not yet know for certain why these individual differences exist or how to predict them. Intra-individual factors may play a role. For example, normative genetic variations have been linked with individual differences in behavioral outcomes (e.g., 138, 139). Likewise, intra-individual behaviors have also been studied; working memory skills have been shown to

moderate the link between early institutional care and mental health outcomes (e.g., attention deficit hyperactivity disorder; separation anxiety symptoms)(140, 141), as have affective processing biases (142). Earlier interventions (i.e., therapy, placement in families) tend to be associated with better affective health for children and adolescents (143–147).

Heterogeneity and intervention following early adversity.

Another source of individual differences may be positive, strength promoting experiences that compete with adverse ones to ameliorate developmental outcomes after adverse experiences. For example, interventions targeting parental nurturance, sensitivity, and threatening behaviors have been shown to causally reduce child problem behavior in high-risk samples (148). This finding is particularly important since parents can be powerful buffers of stress in childhood (149). This positive effect of the parent is especially important to consider in the context of adverse environments, and it has been shown that parental presence can buffer the fear-potentiated startle of children exposed to high levels of violence (150). If human brain development is neotenous, retaining plasticity for a long time, then it might logically extend that positive experiences, even after adversity exposure, might confer additional benefits at older ages (see Figure 1, moments a,b,c). Consistent with this prediction, children and adolescents with a prior history of institutional care show steeper declines in anxiety symptoms in the future if they exhibited a dampening response to (adoptive) parental cues (“buffering”) at the initial time of testing (80). Whether or not children and adolescents exhibit this amygdala dampening in response to their parent is associated with the security they report feeling towards their (adoptive) parent at initial testing. Likewise, greater feelings of security correlate with lower internalizing problems following early institutional care (142), but not in youth with a typical caregiving background (whose scores were near floor levels). This finding suggests that while strong families are always important for emotional development, their effects may be especially visible following early adversity.

Conclusion

Human brain development is optimized to learn from environmental cues. However, this optimization also places infants and children at risk if exposed to adverse caregiving. The link between early caregiving adversity and poor mental health is not deterministic, as there is significant heterogeneity in outcome, and outcomes can change with ameliorative experiences. Nonetheless, the risk is significant. Additionally, while abusive and neglectful caregiving are potent stressors for the developing child, so is the separation of the child from his/her parent. This separation is traumatic, because children form attachments to their parents, even in the context of maltreatment. Therefore, the implications of this research for mental health include using developmentally-informed approaches to understand pathways of emotional development following early adversity, viewing stable caregiving as a basic need during development, and understanding that supporting children’s emotional development means supporting their families as well.

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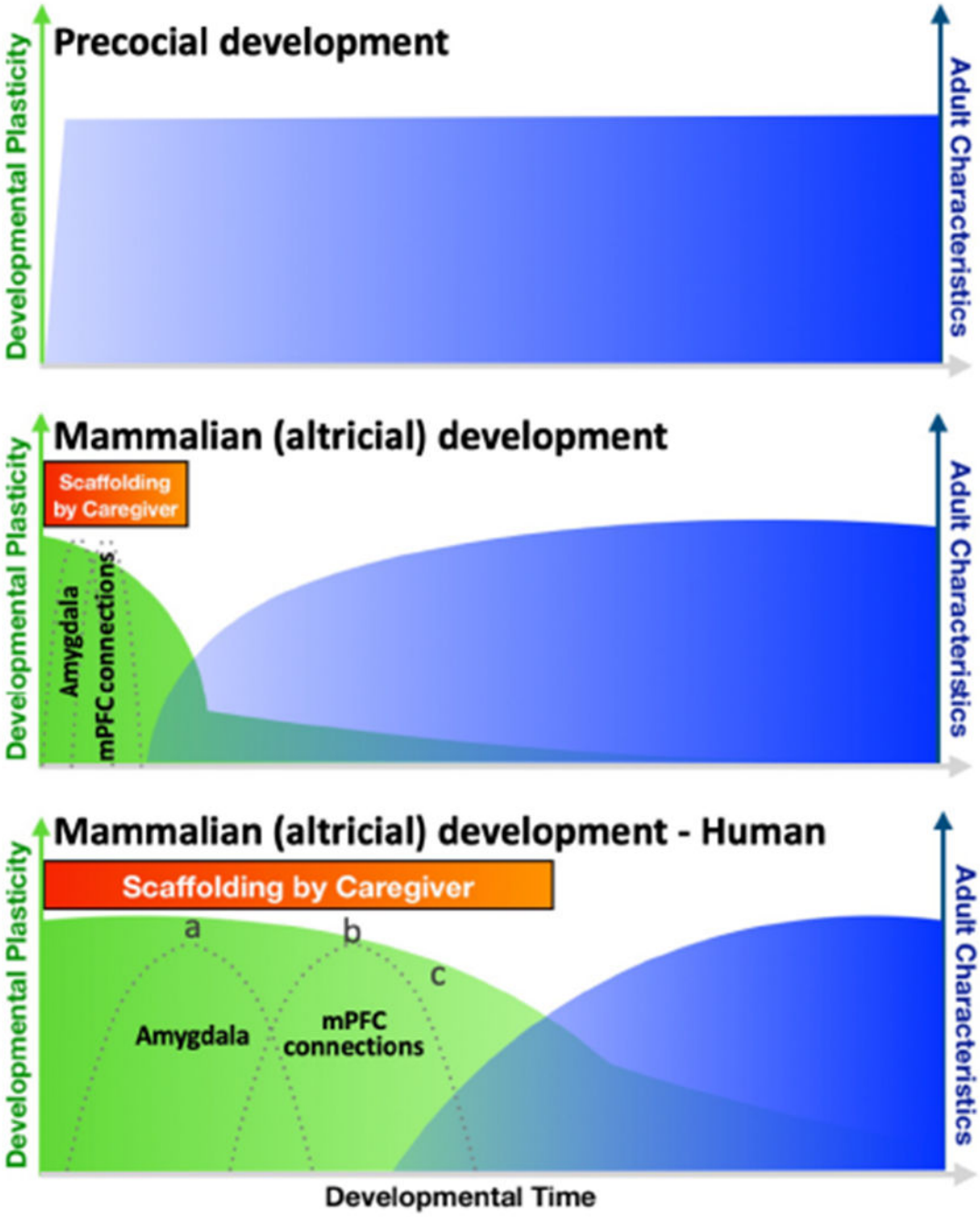

Figure 1.

Neotenous brain development permits increased opportunity to receive caregiver input. Altricial development (bottom two panels), unlike that of precocial species (top panel), requires caregiver input, which satisfies a species-expectation that the caregiving environment will scaffold the offspring's developing neurobiology during periods of high developmental plasticity (green) before circuitry begins to take on adult characteristics (blue). Here, the example of amygdala-medial prefrontal cortex (mPFC) circuit development is used to illustrate how an expansion, and therefore protraction, of developmental processes

enables significant influence from the caregiving environment on developing neurobiology in the case of the human (bottom panel). Dotted lines are meant to represent putative sensitive periods for the amygdala and its connections with mPFC. Interventions (e.g., changes in parenting, therapy) may have differential efficacy depending on when they occur (i.e., moments a,b,c), motivating the development and use of age-specific approaches. Note: 'Developmental Time' on x-axis is intended to be equated across the three species-types (top, middle, and bottom).